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None

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UK CL (Edition K) C2C CTZ CUJ
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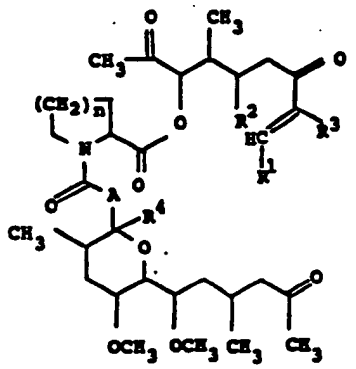
(54) Tetrahydropyrane compounds, a process for their production and a pharmaceutical composition containing the same

(57) Compounds of the formula :



(I)

wherein R^1 is hydroxy and R^2 is hydrogen, hydroxy, alkoxy or acyloxy, or R^1 and R^2 are combined to form oxa,
R^3 is alkyl, ar(lower)alkyl or protected carboxy(lower)alkyl,
R^4 is hydroxy or alkoxy,
A is methylene, hydroxymethylene or carbonyl, and
n is an integer of 1 or 2,
or a pharmaceutically acceptable salt thereof.

A process for the production of these compounds is also described, together with pharmaceutical compositions containing them.

The compounds possess *immunosuppressive* and *antimicrobial properties* and are useful for treatment and prevention of resistance to transplantation, graft-versus-host diseases by medulla ossium transplantation, autoimmune diseases and infectious diseases, for example.

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TETRAHYDROPYRANE COMPOUNDS, A PROCESS FOR THEIR PRODUCTION AND A PHARMACEUTICAL COMPOSITION CONTAINING THE SAME

This invention relates to novel tetrahydropyrane compounds having pharmacological activities, to a process for their production and to a pharmaceutical composition containing the same.

More particularly, it relates to novel tetrahydropyrane compounds, which have pharmacological activities such as immunosuppressive activity, antimicrobial activity, and the like, to a process for their production, to a pharmaceutical composition containing the same and to a use thereof as a medicament.

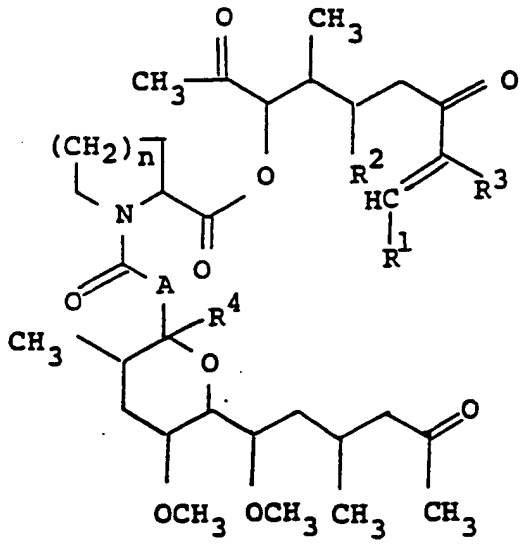
Accordingly, one object of this invention is to provide the novel tetrahydropyrane compounds, which are useful for treatment and prevention of resistance by transplantation, graft-versus-host diseases by medulla ossium transplantation, autoimmun diseases, inf ctious diseases, and the like.

Another obj ct of this invention is to provide a process for production of the tetrahydropyrane compounds by synthetic process.

A further object of this invention is to provide a pharmaceutical composition containing, as active ingredients, the tetrahydropyrane compounds.

Still further object of this invention is to provide a use of the tetrahydropyrane compounds as a medicament for treating and preventing resistance by transplantation, graft-versus-host diseases by medulla ossium transplantation, autoimmune diseases, infectious diseases, and the like.

The new tetrahydropyrane compounds of this invention can be represented by the following general formula :



(I)

wherein R^1 is hydroxy and R^2 is hydrogen, hydroxy, alkoxy or acyloxy, or R^1 and R^2 are combined to form oxa,

R^3 is alkyl, ar(lower)alkyl or protected

carboxy(low r)alkyl,

R^4 is hydroxy or alkoxy,

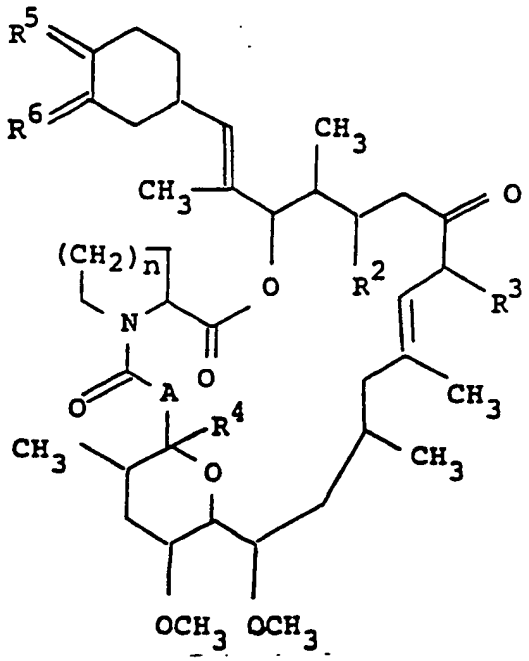
A is methylene, hydroxymethylene or carbonyl, and

n is an integer of 1 or 2.

With respect to the tetrahydropyrane compounds (I) of this invention, it is to be understood that there may be one or more conformer(s) or stereoisomeric pairs such as optical and geometrical isomers due to asymmetric carbon atom(s) and double bond(s), and such isomers are also included within a scope of this invention.

According to this invention, the object tetrahydropyrane compounds (I) can be prepared by the following process.

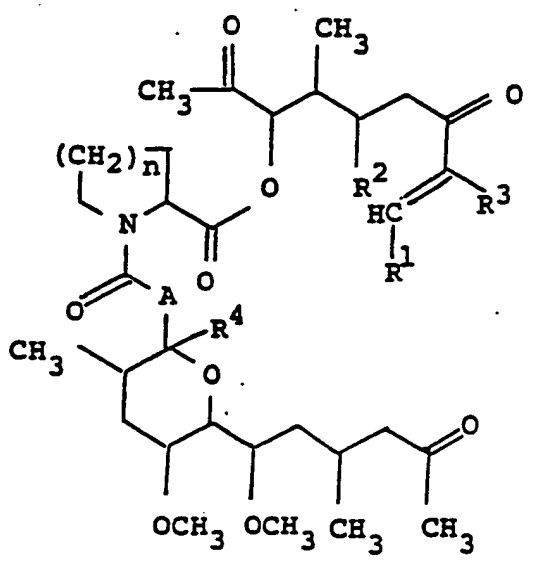
Process



(II)

or a salt thereof

↓ Oxidative Cleavage



(I)

or a salt thereof

in which R^1, R^2, R^3, R^4, A and n are each as defined above,

R^5 and R^6 are each oxo, or (R^5_a, H) and (R^6_a, H) respectively,

wherein R^5_a and R^6_a are each hydroxy, lower alkoxy or $OCH_2OCH_2CH_2OCH_3$, or R^6_a is protected hydroxy, in addition, R^5_a and R^6_a are combined to form oxa.

Particulars of the above definitions and the preferred embodiments thereof are explained in detail as follows.

The term "lower" used in the specification is intended to mean 1 to 6 carbon atoms, unless otherwise indicated.

Suitable "acyl" and acyl group in the "acyloxy" may include aliphatic acyl, aromatic acyl and aliphatic acyl

substituted with aromatic group, which ar derived from carboxylic, sulfonic and carbamic acids; and the like.

The aliphatic acyl may include lower alkanoyl which may have one or more suitable substituent(s) such as carboxy (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, carboxyacetyl, carboxypropionyl, carboxybutyryl, carboxyhexanoyl, etc.), cyclo(lower)alkyloxy(lower)-alkanoyl which may have one or more suitable substituent(s) such as lower alkyl (e.g. cyclopropyloxyacetyl, cyclobutyloxypropionyl, cycloheptyloxybutyryl, menthyloxyacetyl, menthyloxypropionyl, menthyloxybutyryl, menthyloxyheptanoyl, menthyloxyhexanoyl, etc.), camphorsulfonyl, lower alkylcarbamoyl having one or more suitable substituent(s) such as carboxy, protected carboxy and hydroxy for example, carboxy(lower)alkylcarbamoyl (e.g. carboxymethylcarbamoyl, carboxyethylcarbamoyl, carboxypropylcarbamoyl, carboxybutylcarbamoyl, carboxypentylcarbamoyl, carboxyhexylcarbamoyl, etc.), protected carboxy(lower)alkylcarbamoyl such as tri(lower)-alkylsilyl(lower)alkoxycarbonyl(lower)alkylcarbamoyl (e.g. trimethylsilylmethoxycarbonylethylcarbamoyl, trimethylsilylethoxycarbonylpropylcarbamoyl, triethylsilylethoxycarbonylpropylcarbamoyl, tert-butyldimethylsilylethoxycarbonylpropylcarbamoyl, trimethylsilylpropoxycarbonylbutylcarbamoyl, etc.), hydroxy(lower)alkylcarbamoyl (e.g. hydroxymethylcarbamoyl, hydroxyethylcarbamoyl, hydroxypropylcarbamoyl, hydroxybutylcarbamoyl, hydroxypentylcarbamoyl, hydroxyhexylcarbamoyl, etc.), and the like.

The aromatic acyl may include aroyl which may hav one r mor suitable substituent(s) such as nitro (.g.

benzoyl, toluoyl, xyloyl, naphthoyl, nitr benzoyl, dinitrobenzoyl, nitronaphthoyl, etc.), arenesulfonyl which may have one or more suitable substituent(s) such as halogen (e.g. benzenesulfonyl, toluenesulfonyl, xylenesulfonyl, naphthalenesulfonyl, fluorobenzenesulfonyl, chlorobenzenesulfonyl, bromobenzenesulfonyl, iodobenzenesulfonyl, etc.), arylcarbamoyl which may have one or more suitable substituent(s) such as halogen (e.g. phenylcarbamoyl, fluorophenylcarbamoyl, chlorophenylcarbamoyl, etc.), and the like.

The heterocyclic acyl may include heterocyclic carbonyl (e.g. furoyl, thenoyl, nicotinoyl, isonicotinoyl, thiazolylcarbonyl, thiadiazolylcarbonyl, tetrazolylcarbonyl, morpholinocarbonyl, etc.), and the like.

The aliphatic acyl substituted with aromatic group may include ar(lower)alkanoyl which may have one or more suitable substituent(s) such as lower alkoxy and trihalo(lower)alkyl (e.g. phenylacetyl, phenylpropionyl, phenylbutyryl, 2-trifluoromethyl-2-methoxy-2-phenylacetyl, 2-ethyl-2-trifluoromethyl-2-phenylacetyl, 2-trifluoromethyl-2-propoxy-2-phenylacetyl, etc.), and the like.

The more preferred acyl group thus defined may be C_1-C_4alkanoyl which may have carboxy, cyclo(C_5-C_6)-alkyloxy(C_1-C_4)alkanoyl having two (C_1-C_4)alkyl groups on the cycloalkyl moiety, camphorsulfonyl, carboxy(C_1-C_4)-alkylcarbamoyl, hydroxy(C_1-C_4)alkylcarbamoyl, tri(C_1-C_4)alkylsilyl(C_1-C_4)alkoxycarbonyl(C_1-C_4)alkyl-carbamoyl, haloarylcarbamoyl, benzoyl which may have one or two nitro, benzenesulfonyl having halog n, phenyl(C_1-C_4)alkanoyl having C_1-C_4alkoxy and

trihalo(C_1-C_4)alkyl, morpholinocarbonyl, and the most preferred one may be acetyl, carboxypropionyl, menthyloxyacetyl, camphorsulfonyl, hydroxypropylcarbamoyl, benzoyl, nitrobenzoyl, dinitrobenzoyl, iodobenzenesulfonyl, phenylcarbamoyl, fluorophenylcarbamoyl, chlorophenylcarbamoyl, 2-trifluoromethyl-2-methoxy-2-phenylacetyl and morpholinocarbonyl.

Suitable "alkoxy" may include straight or branched lower alkoxy such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentoxy, isopentoxy, neopentoxy, hexyloxy and the like, in which the preferred one is C_1-C_4 alkoxy.

Suitable "alkyl" may include straight or branched lower alkyl such as propyl, isopropyl, butyl, isobutyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, and the like, in which more preferred example may be C_1-C_4 alkyl and the most preferred one may be ethyl and propyl.

Suitable "ar(lower)alkyl" may include aforementioned lower alkyl, which is substituted with aryl as mentioned below, wherein more preferred example may be phenyl(C_1-C_4)alkyl.

Suitable "protected carboxy(lower)alkyl" may include aforementioned lower alkyl, which is substituted with protected carboxy as mentioned below, wherein more preferred example may be (C_1-C_4)alkoxycarbonyl(C_1-C_4)-alkyl.

Suitable "protect d carboxy" may include esterified carboxy such as low r alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl,

is pr poxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, etc.), mono(or di or tri)phenyl(lower)alkoxycarbonyl which may have a nitro group (e.g. benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, phenethyloxycarbonyl, benzhydryloxycarbonyl, trityloxycarbonyl, etc.), and the like, in which more preferred example may be C_1-C_4 alkoxycarbonyl.

Suitable "aryl" may include phenyl, tolyl, xylyl, cumenyl, mesityl, naphthyl, and the like, in which the preferred example may be phenyl.

Suitable hydroxy-protective group moiety in the term of "protected hydroxy" means a conventional hydroxy-protective group such as acyl as mentioned above; ar(lower)alkyl such as mono- or di- or triphenyl(lower)-alkyl (e.g. benzyl, benzhydryl, trityl, etc.), etc.; trisubstitutd silyl such as tri(lower)alkylsilyl (e.g. trimethylsilyl, triethylsilyl, isopropyldimethylsilyl, t-butyldimethylsilyl, diisopropylmethylsilyl, etc.), triarylsilyl (e.g. triphenylsilyl, etc.), triar(lower)alkylsilyl (e.g. tribenzylsilyl, etc.), etc.; and the like.

The process for production of tetrahydropyrane compounds (I) of this invention is explained in detail in the following.

Process :

The compounds (I) or a salt thereof can be prepared by subjecting the compounds (II) or a salt thereof to an oxidative cleavage of the olefinic bonds.

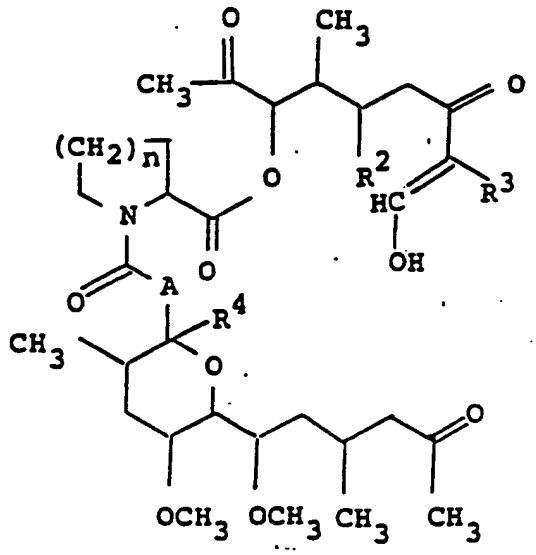
The oxidizing agent applicable to this process may be a conventional one which is capable of cl avaging olefinic b nds to oxo groups, for example, an inorganic peracid or

a salt ther of (e.g. periodic acid, persulfuric acid, r sodium or potassium salt thereof, etc.), an organic peracid or a salt thereof (e.g. perbenzoic acid, m-chloroperbenzoic acid, performic acid, peracetic acid, chloroperacetic acid, trifluoroperacetic acid, or sodium or potassium salt thereof, etc.), a combination of ozone and dimethyl sulfide, hydrogen peroxide, urea-hydrogen peroxide, N-halosuccinimide (e.g., N-bromosuccinimide, N-chlorosuccinimide, etc.), hypochlorite compound (e.g. tert-butyl hypochlorite, etc.), permanganate (e.g. potassium permanganate, etc.), chrome compound such as chromium trioxide pyridine, chromium trioxide-sulfuric acid, alkali metal dichromate (e.g. sodium dichromate, potassium dichromate, etc.), lower alkyl chromate (e.g. t-butyl chromate, etc.), and the like.

This reaction is usually conducted in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, pyridine, ethyl acetate, N,N-dimethylformamide, dichloromethane, ethyl ether, isopropyl ether, 1,4-dioxane, or a mixture thereof.

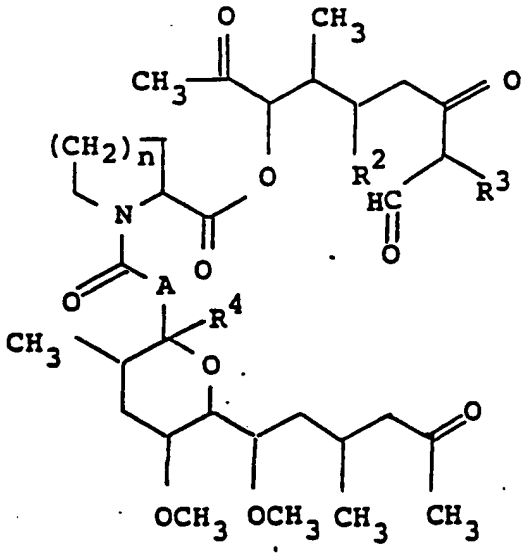
The reaction temperature is not critical and the reaction is usually conducted under from cooling to warming.

With regard to the compounds (I), in case of R^1 being hydroxy, it is to be noted that the following formula (Ia) is well known to lie in a tautomeric relation with the following formula (Ib), and accordingly the both of them are substantially the same.



(Ia)

Tautomerism



(Ib)

All f th above tautomeric isomers are included within the scope of the present invention, and in the present specification, however, the compounds including such tautomiric isomers are represented by using one of the expressions therefor, i.e. the formula (Ia) and the nomenclature corresponding to it.

The object tetrahydropyrane compounds (I) obtained according to the process as explained above can be isolated and purified in a conventional manner, for example, extraction, precipitation, fractional crystallization, recrystallization, chromatography, an the like.

Suitable salts of the compounds (I) and (II) may include pharmaceutically acceptable salts such as basic salts, for example, alkali metal salt (e.g. sodium salt, potassium salt, etc.), alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), ammonium salt, amine salt (e.g. triethylamine salt, N-benzyl-N-methylamine salt, etc.) and other conventional organic salts.

With respect to the tetrahydropyrane compounds (II) of this invention, it is to be understood that there may be one or more conformer(s) or stereoisomeric pairs such as optical and geometrical isomers due to asymmetric carbon atom(s) and double bond(s), and such isomers are also included within a scope of this invention.

The starting compounds (II) in the process mentioned above contains known and novel compounds, and the known compounds are disclosed, for example, in European Patent Publication Nos. 184162 and 323042, and the new compound can be prepared by a conventional manner.

PHARMACOLOGICAL ACTIVITIES OF THE TRICYCLO COMPOUNDS

The tetrahydropyran compounds (I) poss ss pharmacological activities such as immunosuppressive activity, antimicrobial activity, and the like, and therefore are useful for the treatment and prevention of the resistance by transplantation of organs or tissues such as heart, kidney, liver, medulla ossium, skin, cornea etc., graft-versus-host diseases by medulla ossium transplantation, autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes, uveitis such as Behcet's disease, etc., vernal keratoconjunctivitis, infectious diseases caused by pathogenic microorganisms, and the like.

And further, the tetrahydropyrane compounds (I) are also useful in the topical administration for the treatment and the prophylaxis of inflammatory and hyperproliferative skin diseases and cutaneous manifestations of immunologically-mediated illnesses, such as, psoriasis, atopical dermatitis, contact dermatitis and further eczematous dermatitises, seborrhoeis dermatitis, Lichen planus, Pemphigus, bullous Pemphigoid, Epidermolysis bullosa, urticaria, angoiedemas, vasculitides, erythemas, cutaneous eosinophilias, Lupus erythematosus and Alopecia areata.

The pharmaceutical composition of this invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains the tetrahydropyrane compounds (I), as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral or parenteral applications. The active ingredient may be comp unded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets,

capsules, supp sitori s, solutions, emulsi ns, suspensions, injections, ointments, liniments, eye drops lotion, gel, creme and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening, solubilizing an coloring agents and perfumes may be used. Particularly, as a solubilizing agent, there may be exemplified water-soluble cellulose polymer (i.e. hydroxypropyl methylcellulose, etc.), water-soluble glycol (i.e. propylene glycol, etc.), etc. The active object compound is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of diseases.

For applying this composition to human, it is preferable to apply it by parenteral or enteral administration. While the dosage of therapeutically effective amount of the tetrahydropyrane compounds (I) varies from and also depends upon the age and condition of each individual patient to be treated, a daily dose of about 0.01-1000 mg, preferably 0.1-500 mg and more preferably 0.5-100 mg, of the active ingredient is generally given for treating diseases, and an average single dose of about 0.5 mg, 1 mg, 5 mg, 10 mg, 50 mg, 100 mg, 250 mg and 500 mg is generally administered.

The following examples are given for the purpose of illustrating the present invention.

Example 1

A solution of 1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1methylvinyl]23,25-dimethoxy-13,19,21,27-tetramethyl-17—propyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]oxtacos-18—ene-2,3,10,16-tetraone (540 mg) in a mixture of ethanol (0.05 ml) and dichloromethane (11 ml) was passed through ozone for 10 minutes at -78°C. After bubbling with nitrogen, the reaction mixture was stirred for 30 minutes at ambient temperature. Then excess dimethyl sulfide (ca. 1 ml) was added to this mixture and this solution was stirred for additional 2 hours. The solution was concentrated in vacuo, and the residue was purified by a column chromatography (ether-hexane = 4:1) to give a residue (240 mg). This residue was further purified by a preparative thin layer chromatography (ethyl acetate-hexane = 1:1) to give pure 2-{2-[1-acetyl-2-(2,3-dihydro-4-oxo-5-propyl-pyran-2-yl)propyloxycarbonyl]-piperidinooxalyl}-2-hydroxy-5-methoxy-6-(1-methoxy-3-methyl-5-oxohexyl)-3-methyltetra-hydropyrane (30 mg).

MS : 716 (M^+ +Na)

Example 2

2-{2-[1-Acetyl-2-(5-ethyl-2,3-dihydro-4-oxopyran-2-yl)propyloxycarbonyl]piperidinooxalyl}-2-hydroxy-5-methoxy-6-(1-methoxy-3-methyl-5-oxohexyl)-3-methyl-tetrahydropyrane was obtained in 34.9% yield in substantially the same manner as that of Example 1.

MS : 702 (M^+ + Na)

Example 3

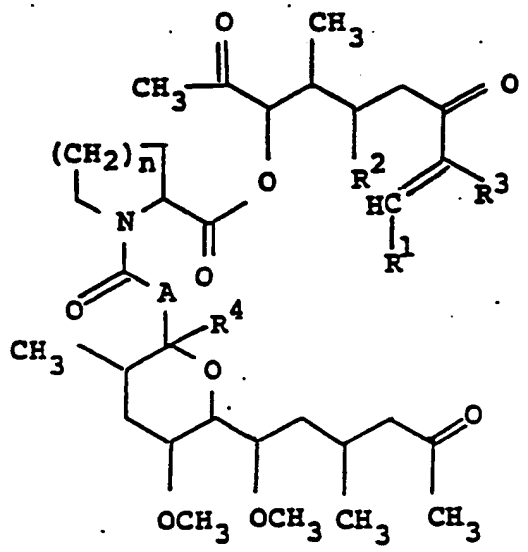
2-[2-(1-Acetyl-6-hydroxymethylidene-2-methyl-5-oxononyloxycarbonyl)piperidinooxalyl]-2-hydroxy-3-methyl-6-(3-methyl-1-methoxy-5-oxohexyl)-5-methoxytetrahydro-

pyrane was obtained in 18.9% yield in substantially the same manner as that of Example 1.

^{13}C-NMR ($CDCl_3$, δ) : 208.8 (208.5), 204.1 (204.7), 198.9 (198.6), 197.0 (193.7), 170.2 (169.7), 165.6 (166.7), 158.7 (159.0), 121.6

What is claim is :

1. A compound of the formula :



(I)

wherein R^1 is hydroxy and R^2 is hydrogen, hydroxy, alkoxy or acyloxy, or R^1 and R^2 are combined to form oxa,

R^3 is alkyl, ar(lower)alkyl or protected carboxy(lower)alkyl,

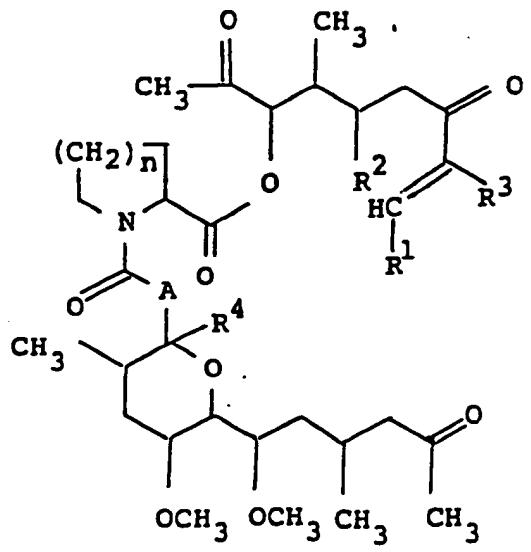
R^4 is hydroxy or alkoxy,

A is methylene, hydroxymethylene or carbonyl, and

n is an integer of 1 or 2,

or a pharmaceutically acceptable salt thereof.

2. A process for the preparation of a compound of the formula :



(I)

wherein R^1 is hydroxy and R^2 is hydrogen, hydroxy, alkoxy or acyloxy, or R^1 and R^2 are combined to form oxa,

R^3 is alkyl, ar(lower)alkyl or protected carboxy(lower)alkyl,

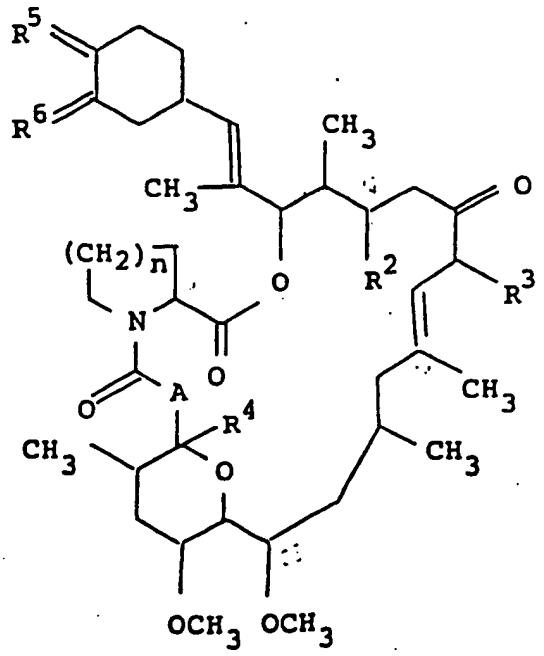
R^4 is hydroxy or alkoxy,

A is methylene, hydroxymethylene or carbonyl, and

n is an integer of 1 or 2,

or a salt thereof,

which comprises subjecting a compound of the formula :



(II)

wher in R^1, R^2, R^3, R^4, A and n ar each as defined abov ,
R^5 and R^6 are each oxo, or (R_a^5, H) and (R_a^6, H) respectively,
wherein R_a^5 and R_a^6 are each hydroxy, lower alkoxy or $OCH_2OCH_2CH_2OCH_3$, or R_a^6 is protected hydroxy, in addition, R_a^5 and R_a^6 are combined to form oxa,
or a salt thereof to oxidative cleavage of the olefinic bonds.

3. A pharmaceutical composition containing the compounds of claim 1, as an active ingredient, in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

4. A use of the compounds of claim 1 as a medicament.

5. A method for treating or preventing resistance by transplantation, graft-versus-host diseases by medulla ossium, autoimmune diseases and infectious diseases which comprises administering the compound of claim 1 to human or animal.

6. The compounds of Claim 1 for use as a medicament.

7. A use of the compound of Claim 1 for manufacturing a medicament for treating or preventing resistance by transplantation, graft-versus-host diseases by medulla ossium, autoimmune diseases and infectious diseases.

8. A process for pr paring a pharmaceutical composition which comprises admixing the compound of Claim 1 with a pharmac utically acceptabl carrier r excipient.

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